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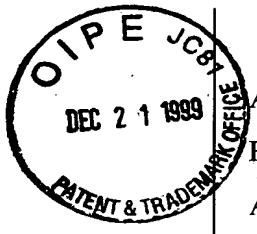

In re application of:
PRICE *et al.*
Appl. No. 09/390,634
Filed: September 7, 1999
For: **Method for Expanding Embryonic Stem Cells in Serum-Free Culture**

Art Unit: 1651
Examiner: To be assigned
Atty. Docket: 0942.4190002/RWE/GER

Information Disclosure Statement

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

Following is information that may be considered material to the examination of this application, in compliance with the duty of disclosure requirements of 37 C.F.R. §§ 1.56, 1.97 and 1.98.

I. Documents Listed On The Attached Form PTO-1449

A copy of each of listed documents AN2, AR1, AS8, AS11, and AS19 is provided herewith. The other listed documents were cited on the Form PTO-892 or the Form PTO-1449 in Applicants' 35 U.S.C. § 120 priority Application No. 08/781,772, filed January 10, 1997, and a copy of each of those documents can be found in the Patent Office file for Application No. 08/781,772.

For the Examiner's convenience, a copy of each of listed documents AS22, AT22, AR23, AS23, AT23 and AR24 is provided herewith. The dates on listed documents AS22, AT22, AR23, AS23, AT23 and AR24 have been masked.

Where the publication date of a listed document does not provide a month of publication, the year of publication of the listed document is sufficiently earlier than the effective U.S. filing date and any foreign priority date so that the month of publication is not in issue. Applicants have listed publication dates on the attached PTO-1449 based on information presently available to the undersigned. However, the listed publication dates should not be construed as an admission that the information was actually published on the date indicated.

II. Co-Pending Applications

The Examiner is also referred to the following co-pending patent applications:

U.S. Application No. 08/792,299, filed January 31, 1997;

U.S. Application No. 08/948,053, filed October 9, 1997;

U.S. Application No. 08/949,142, filed October 10, 1997;

U.S. Application No. 09/028,514, filed February 23,1998;

U.S. Application No. 09/023,790, filed February 13, 1998; and

U.S. Application No. 09/302,953, filed April 30, 1999.

The identification of these U.S. patent applications is not to be construed as a waiver of secrecy as to these applications now or upon issuance of the present application as a patent. The Examiner is respectfully requested to consider the cited applications and the art cited therein during examination.

III. Statement of Facts for Consideration by the Examiner

A. Introduction

This application is a divisional of Application No. 08/781,772, filed January 10, 1997. More than one year prior to January 10, 1997, Dr. Mindy Goldsborough, one of the listed inventors, and her colleagues at Life Technologies, Inc., the assignee of the above-captioned application, developed a claimed serum-free supplement and determined that it would support the growth of embryonic stem cells, in serum free culture, when cultured with feeder cells. More than one year prior to January 10, 1997, Dr. Goldsborough wished to determine whether embryonic stem cells cultured in a medium supplemented with the serum-free supplement would support the production of transgenic animals. Because Dr. Goldsborough and her colleagues at Life Technologies, Inc. did not have access to facilities that were required to perform transgenic animal research, Dr. Goldsborough arranged to have two scientists outside of Life Technologies, Inc. perform transgenic animal experiments.

About 10 established embryonic stem cell lines are used by researchers to perform embryonic stem cell research, such as the production of transgenic animals. Some of these lines are leukemia inhibitory factor (LIF)-dependent, and some of these lines are LIF-independent. More than one year prior to January 10, 1997, Dr. Goldsborough arranged to have Dr. Mary Stevens, at the Lawrence Berkeley Laboratory, perform experiments using a LIF-dependent embryonic stem cell line. More than one year prior to January 10, 1997, Dr. Goldsborough also arranged to have Dr. Beverly Koller, at the University of North Carolina, perform experiments using an LIF-independent embryonic stem cell line.

B. Experimental Work Performed by Dr. Mary Stevens

More than one year prior to January 10, 1997, Dr. Goldsborough contacted Dr. Stevens and asked Dr. Stevens to provide Dr. Goldsborough with a cost estimate for performing experiments in which medium supplemented with the claimed serum-free supplement would be used to culture LIF-dependent embryonic stem cells, blastocysts would be injected with the cultured cells, and the development of transgenic mice would be attempted. Control, LIF-dependent cells would be cultured in a serum-containing medium, injected into blastocysts, and the development of transgenic mice would be attempted.

More than one year prior to January 10, 1997, Dr. Stevens provided Dr. Goldsborough with a cost estimate for performing the experiments. A copy of Dr. Steven's facsimile transmission to Dr. Goldsborough is listed as document AS22 on the attached Form PTO-1449. At page 1 of document AS22, Dr. Stevens wrote: "John says we need more feeder cells to do this. Can you send more w/LIF and serum supplement?" "LIF" refers to leukemia inhibitory factor. Dr. Goldsborough had previously provided Dr. Stevens with feeder cells to use in experiments separate from experiments performed using the claimed serum-free supplement. Dr. Stevens had not yet been provided with any samples of the claimed serum-free supplement. Dr. Goldsborough had also agreed to provide Dr. Stevens with LIF. Thus, when Dr. Stevens wrote "Can you send more w/LIF and serum supplement," Dr. Stevens was asking for more feeder cells to be sent with the LIF and the first sample of the serum-free supplement, and not for more LIF or for more of the claimed serum-free supplement.

More than one year prior to January 10, 1997, Dr. Goldsborough provided Dr. Stevens with a sample of a claimed serum-free medium supplement. More than one year prior to January 10, 1997, in accordance with Dr. Goldsborough's instructions, Dr. Stevens's staff cultured embryonic stem cells from an LIF-dependent embryonic stem cell line in a medium supplemented with the claimed serum free supplement. Control cells were cultured in a medium supplemented with serum. The cultured cells were injected into blastocysts, and the blastocysts were transplanted into female mice. Cells cultured in the serum-containing control medium produced healthy litters in both of two transplanted mothers. In the three animals that were transplanted with blastocysts containing cells cultured in the medium supplemented with the claimed serum-free supplement, none of the animals produced litters.

More than one year prior to January 10, 1997, utilizing the same sample of a claimed serum-free supplement, Dr. Stevens's staff performed a second round of cell culture, blastocyst injection, and transplantation. More than one year prior to January 10, 1997, Dr. Stevens reported to Dr. Goldsborough the results of the cell culture phase of the experiment and of blastocyst injection data. A copy of Dr. Steven's facsimile transmission to Dr. Goldsborough is listed as document AT22 on the attached Form PTO-1449. This document was dated more than one year prior to January 10, 1997. At page 6 of document AT22, Dr. Stevens explained that all of the chimeric animals described at page 6 had been mated with C57/DBA mice to test for germline transmission. Thereafter, but more than one year before January 10, 1997, Dr. Stevens reported the results of the mating experiments to Dr. Goldsborough. A copy of Dr. Stevens' report is listed as document AR23 on the attached Form PTO-1449.

Dr. Goldsborough agreed to pay Dr. Stevens for her services in the form of a product credit. A credit account was opened at Life Technologies, Inc. more than one year prior to January 10, 1997. No sale of a claimed serum-free medium supplement occurred and no offers for sale were made to Dr. Stevens or to Lawrence Berkley Laboratories.

Less than one year prior to the January 10, 1997 filing date of the above-identified application, Dr. Goldsborough provided Dr. Stevens with a new sample of a claimed serum-free medium supplement. A copy of a letter from Dr. Goldsborough to Dr. Stevens is listed as document AS23 on the attached Form PTO-1449. This letter was dated less than one year prior to January 10, 1997. In the letter, Dr. Golsborough explained:

> As we discussed, I will be shipping to you today, a sample of LTI's experimental stem cell media supplement. This sample is identical to the earlier sample shipped to you in [date redacted].
>
> In order to confirm both receipt of the sample and of our understandings with regard to these samples, please sign in the space below and return a copy of this letter to my attention.
>
> You understand that the stem cell media supplement is proprietary and confidential to LTI, and that LTI's provision of both this and the earlier sample are conditioned on your agreement to treat both the samples as such. You also understand that both samples are provided for testing purposes only, and that the transfer of these samples is not a sale nor an offer to sell the stem cell media supplement to you in the future.
>
> As with any experimental product, you will use all appropriate safety measures in your storage and use of the samples, and comply with all applicable regulations and laws.

Dr. Stevens signed the letter and returned a copy to Dr. Goldsborough. A copy of the letter, signed by Dr. Stevens, is listed as document AT23 on the enclosed Form PTO-1449. Thus, by signing the letter, Dr. Stevens confirmed her understanding that the sample provided to her more than one year prior to January 10, 1997 and the sample provided to her less than one year prior to January 10, 1997 (a) were proprietary and confidential to Life

Technologies, Inc., (b) were provided for testing purposes only, and (c) were not sold or offered for sale.

C. Experimental Work Performed by Dr. Beverly Koller

As explained above, Dr. Stevens's experiments were performed using an embryonic stem cell line that is LIF-dependent. Dr. Goldsborough and her colleagues at Life Technologies, Inc. wished to determine whether LIF-independent embryonic stem cells that were cultured in medium supplemented with a claimed serum-free supplement would support the production of transgenic animals. More than one year prior to January 10, 1997, Dr. Goldsborough contacted Dr. Beverly Koller, of the University of North Carolina, and asked Dr. Koller to provide Dr. Goldsborough with a cost estimate for performing experiments in which medium supplemented with a claimed serum-free supplement would be used to culture LIF-independent embryonic stem cells, blastocysts would be injected with the cultured cells, and the development of transgenic mice would be attempted. Control LIF-independent embryonic stem cells would be cultured in a serum-containing medium, injected into blastocysts, and the development of transgenic mice would be attempted.

More than one year prior to January 10, 1997, Anne Latour, a member of Dr. Koller's laboratory, provided Dr. Goldsborough with a cost estimate for performing the experiments. A copy of Ms. Latour's facsimile transmission to Dr. Goldsborough is listed as document AR24 on the attached Form PTO-1449. This document was dated more than one year prior to January 10, 1997.

More than one year prior to January 10, 1997, Dr. Goldsborough agreed to pay Dr. Koller for her services in the form of a product credit. A credit account was opened at Life Technologies more than one year prior to January 10, 1997. No sale of a claimed medium supplement occurred and no offers for sale were made to Dr. Koller or to the University of North Carolina.

More than one year prior to January 10, 1997, Dr. Goldsborough provided Dr. Koller with a sample of a claimed serum-free medium supplement. More than one year prior to January 10, 1997, Dr. Goldsborough encountered technical problems with feeder cell attachment and embryonic stem cell colony size. Before Dr. Koller had performed any experiments, Dr. Goldsborough instructed Dr. Koller to destroy the entire sample of the claimed serum-free supplement.

IV. Additional Comments

Applicants reserve the right to establish the patentability of the claimed invention over any of the information provided herewith, and/or to prove that this information may not be prior art, and/or to prove that this information may not be enabling for the teachings purportedly offered.

This Information Disclosure Statement should not be construed as a representation that a search has been made, or that information more material to the examination of the present patent application does not exist. The Examiner is specifically requested not to rely solely on the material submitted herewith. It is further understood that the Examiner will consider information that was cited or submitted to the U.S. Patent and Trademark Office in a prior application relied on under 35 U.S.C. § 120. 1138 OG 37, 38 (May 19, 1992).

This Information Disclosure Statement is being filed before the mailing of a first Office Action on the merits. Accordingly, no statement or fee is required.

Applicants respectfully request that the Examiner initial and return a copy of the enclosed PTO-1449 and indicate in the official file wrapper of this patent application that the documents have been considered. The U.S. Patent and Trademark Office is hereby authorized to charge any fee deficiency, or credit any overpayment, to our Deposit Account No. 19-0036.

Respectfully submitted,

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